THE VALUE OF THE CAMMIDGE REACTION IN THE DIAGNOSIS OF PANCREATIC DISEASE.*

FROM THE PRIVATE LABORATORY OF DR. JOHN H. MUSSER.

BY EDWARD H. GOODMAN, M.D.,

OF PHILADELPHIA,

Assistant Instructor in Medicine, University of Pennsylvania; Dispensary Physician, Presbyterian Hospital.

THE diagnosis of pancreatic disease is usually a matter of the greatest difficulty, and any symptom, sign, or test which is suggested as an aid to our diagnostic equipment, should be given a thorough trial before it is accepted or discarded.

Great assistance has already been given by the laboratory worker, for the most part from the study of the fæces, though strangely enough the urine has been grossly neglected. Glycosuria has been urged as a symptom of pancreatic disease, but its absence in the majority of cases robs it of any diagnostic importance, and the same may be said of the other, almost forgotten, urinary findings.

In the Arris and Gale Lecture for 1904, Cammidge [1] reported the result of his extensive research on pancreatic disease, and described a new laboratory test which he claimed to be of great value in diagnosing pancreatic lesions. Based on the fact that acute and gangrenous pancreatitis are usually associated with fat necrosis, and chronic pancreatitis not infrequently, Cammidge believed that even in the latter condition when there was no visible sign of fat splitting, there might still be some change in the chemical composition of the blood. This change he believed might be due to glycerin, but after a few unsatisfactory examinations of the blood for this substance or its derivatives, he devoted his attention to the study of the urine. At this time he made use of two tests, the A and B reactions. Cammidge believed that in certain diseases of the

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pancreas the formation of crystals with the A reaction could be prevented by preliminary treatment of the urine with mercuric chloride, and this formed the basis of the B reaction.

The very unscientific claims urged for the method by Cammidge, and the insufficient grounds for most of these claims, called forth a storm of criticism from subsequent observers (Ham and Cleland,[2] Schroeder,[3] Gruner,[4] Willcox,[5] and Haldane[6]) and the pancreatic reaction as first described, has fallen into almost universal disrepute.

To render the test free of the personal bias of the investigator, Cammidge[7] has modified his reaction, making the technic a little more complicated, but at the same time making the result an absolute one. This third reaction has been named by him "improved method" or "C" reaction, and is the one I have used in the present series of cases.

A portion of the twenty-four hours' urine, or a portion of the mixed night and morning specimens, is examined for albumin and sugar. If albumin is present it is removed by boiling with the addition of a few drops of acetic acid, cooled and filtered. The removal of the sugar will be spoken of later. To 40 c.c. of the filtered, albumin-free, acid-urine are added 2 c.c. of concentrated hydrochloric acid, and the mixture gently boiled on the sand bath for ten minutes following the first evidence of ebullition. A small flask, with a funnel as a condenser, is used for the purpose. After ten minutes' boiling the flask is removed from the sand bath, cooled in a stream of running water, and the contents made up to 40 c.c. with distilled water; 8 Gm. of lead carbonate are then added to neutralize the excess of acid, and after standing a few minutes the flask is again cooled in running water, and the contents filtered through a moistened, close-grained filter-paper.*

At this stage of the procedure, if sugar has been found on qualitative analysis, a portion of yeast is added to the clear filtrate, and the flask placed in the incubator over night. The next morning the solution is filtered and the test is continued.

*I have found the most satisfactory paper to be Schleicher & Schüll 589 Blue Ribbon.

The acid filtrate is thoroughly shaken with 8 Gm. of tribasic lead acetate, and the precipitate removed by repeated filtration through a well moistened, close grained filter-paper. To get rid of the excess of lead, 4 Gm. of powdered sodium sulphate are added, the mixture heated on a wire gauze to the boiling point, cooled in running water to as low a temperature as possible, and the precipitate removed by careful filtration. Ten c.c. of the filtrate are put in a small flask, made to 17 c.c. with distilled water, and to this are added 0.8 Gm. of phenylhydrazin hydrochloride, 2 Gm. sodium acetate, and 1 c.c. of 50 per cent. acetic acid. The flask is then fitted with a funnel condenser and gently boiled on the sand bath for ten minutes, at the expiration of which time it is filtered hot through a filter-paper moistened with hot water. The filtrate if necessary is made up to 15 c.c. with hot distilled water, and the whole well stirred with a glass rod.

"In well-marked cases of pancreatic inflammation a light-yellow, flocculent precipitate should appear in a few hours, but in less characteristic cases it may be necessary to leave the preparation over night before a deposit occurs. Under the microscope the precipitate is seen to consist of long, light-yellow, flexible, hair-like crystals arranged in delicate sheaves, which, when irrigated with 33 per cent. sulphuric acid, melt away and disappear in ten to fifteen seconds after the acid first touches them. The preparation must always be examined microscopically, as a small deposit may be easily overlooked with the naked eye, and it is also difficult to determine the exact nature of a slight precipitate by macroscopical investigation alone." (Cammidge, *loc cit.*, p. 253.)

The nature of the phenylhydrazin precipitate is unknown, though Cammidge believes that the body is a pentose, not preformed but obtained by hydrolysis. To quote his words (*loc. cit.*, p. 251), "We are not in a position to make any definite statements with regard to the nature of the mother-substance from which the sugar is derived, but our earlier experiments proved that it was not the so-called animal gum of the urine, and the fact that a positive reaction has not, so

far, been obtained by the 'improved method' with the urine, from any but pancreatic cases, suggests that it is probably a body resulting from change in the pancreas, and possibly derived directly from that organ. The relatively large proportion of pentose-yielding material in the pancreas (2.48 per cent.) . . . points to the pancreas as the most likely source. It cannot be denied, however, that the disintegration of other tissue may also at times influence the urine in this respect, and it has also to be remembered that the ingestion of large amounts of pentose-containing food-materials may also cause small quantities of pentose to be excreted in the urine. Therefore while we maintain that a positive reaction by the 'improved method' of performing the so-called 'pancreatic reaction' is strongly suggestive of inflammatory disease of the pancreas, we are not prepared to contend that it is pathognomic of pancreatitis."

Cammidge's present attitude toward his reaction seems to be a very fair one, as the last sentence of the above quotation indicates. He has made 250 consecutive examinations, of which 125 were negative. These negative reactions were observed in 50 normal cases, 92 miscellaneous cases concerning which no further information is given, 10 cases of gall-stone in common duct, 11 cases of gall-stones in gall-bladder, both conditions unassociated with pancreatitis, and 12 cases of cancer of the pancreas. Two cases of acute pancreatitis gave a positive reaction. There were no negative findings in cases of chronic pancreatitis *sui generis* or of pancreatitis accompanied by gall-stones.

Control work on this "C" reaction has been slow in forthcoming, probably on account of the adverse criticism aroused by the previous reactions.

Watson [8] in a series of 250 analyses from 120 consecutive cases found the reaction positive in such cases as acute and chronic pancreatitis, acute suppurative appendicitis and peritonitis, malaria (jaundice with epigastric tenderness) pneumonia (arteriosclerosis), alimentary glycosuria and constipation, duodenal ulcer and chronic pancreatitis, gall-stones in common duct (pancreas inflamed), pregnancy (alimentary

glycosuria), mitral stenosis (inflammatory disease of pancreas), uræmia, colitis, gout, tuberculous enteritis, constipation, chronic nephritis, cerebral hemorrhage, exophthalmic goitre, gastric ulcer, malignant disease of stomach, leukæmia, chronic bronchitis, arteriosclerosis, nephritis, simple catarrhal jaundice, and lymphosarcoma.

This is a startling variety of conditions and would tend to invalidate Cammidge's claims. Watson arranges the cases giving a positive reaction in the following three sub-divisions:

1. A group in which there is a definite clinical or pathological evidence of serious organic disease of the pancreas, for example, acute and chronic pancreatitis, usually associated with disease of the bile-ducts.

2. A group in which the reaction in the urine is associated with pronounced arteriosclerosis, a condition usually accompanied by more or less sclerosis in different glands.

3. A group in which the reaction is dependent on congestion and catarrhal conditions of the gland duct and substance, with associated toxæmia, for example, advanced heart disease, appendicitis, pneumonia, malaria, and the like.

Despite the many varying disorders which give a positive pancreatic reaction Watson believes the test will prove of great value to physicians and surgeons in the diagnosis and treatment of pancreatic disease.

Edgecombe [9] publishes the report of an interesting case of mumps in which, owing to abdominal pain and tenderness with vomiting, an examination of the urine for the pancreatic reaction was undertaken. Cammidge himself conducted the observation and diagnosed "an active inflammation of the pancreas" based on a positive pancreatic reaction.

Schroeder [10] found a positive reaction in chronic pancreatitis, cancer of the pancreas, cancer of stomach, gall-stones, catarrhal jaundice, tuberculous peritonitis, and tumor of upper abdomen, probably of pancreas. Negative findings were seen in chronic pancreatitis, cancer of stomach, abscess of pancreas, gall-stones (three of four cases), catarrhal jaundice (three of four cases), cancer of liver, cholecystitis, and pulmonary tuberculosis. His conclusions are as follows:

1. It has been proved that inflammatory and destructive diseases of the pancreas may give rise to the appearance of certain as yet undefined bodies in the urine, belonging possibly to the sugars or related compounds.

2. The reaction is not pathognomonic for disease of the pancreas in the clinical sense.

3. Extensive clinical observation on the urine in pancreatic and other diseases must finally determine the value of the pancreatic reaction.

In making my observations on the pancreatic reaction, I purposely chose to exclude examination of any normal cases, as Cammidge has reported 50 normal urines of which none gave a positive reaction. I have so far examined 62 individual cases. In several of these, control-examinations were made, which I have not enumerated. The majority of these cases were from the practice of Dr. Musser, but additional cases were furnished me by Dr. J. B. Deaver, Dr. W. Wayne Babcock, Dr. Joseph Sailer, and Dr. Warfield T. Longcope, all of whom I wish to thank for their courtesy. Great kindness has been shown me by Drs. Sailer and Speese in allowing me to study the urines of their cases of experimental pancreatitis. Full details of these are omitted, as the question of the value of the Cammidge reaction based on experimental and pathological work will be presented in a subsequent paper in conjunction with Dr. Speese.

My series includes only abdominal disorders, and I have tried to select several cases presenting the same disease, as a means of control. The list includes acute experimental pancreatitis, acute pancreatitis, chronic pancreatitis, cancer of the pancreas, cirrhosis of the liver, cancer of the gall-bladder and liver, cholecystitis, cholangeitis, gall-stones, cancer of the stomach including cases of mural, pyloric, and cardiac carcinomata, gastric ulcer, gastritis, hyperchlorhydria, gastroptosis, enteritis, renal calculus, fibroid of uterus, autointoxication, and diabetes mellitus. These cases I have tried to arrange in a consistent table, but the combination of several diseases has prevented a systematic classification.

	No.	Pos.	Neg.
Experimental pancreatitis (acute)	4	2	2
Acute pancreatitis	1	1	0
Chronic pancreatitis	2	2	0
Carcinoma of the pancreas	1	0	1
Carcinoma of the stomach and pancreas	2	1	1
Carcinoma of pylorus	3	0	3
Carcinoma of stomach wall	1	0	1
Carcinoma of cardia	1	0	1
Sarcoma of stomach	1	0	1
Gastric ulcer	2	0	2
Hyperchlorhydria	1	0	1
Gastroptosis	1	1	0
Gastritis	2	0	2
Cirrhosis of liver	10	0	10
Carcinoma of gall-bladder	2	0	2
Cholecystitis	4	0	4
Cholangeitis	1	0	1
Gall-stones	2	2	0
Enteritis	1	0	1
Abdominal tumor of obscure origin	1	0	1
Renal calculus	1	0	1
Fibroid of the uterus	1	0	1
Autointoxication	2	0	2
Diabetes mellitus	14	1	13
Myocarditis	1	0	1

Of the 62 cases studied, but ten cases gave a positive Cammidge reaction and in six of these the diagnosis of a pancreatic lesion was confirmed at operation. The case of acute pancreatitis died with all the classical symptoms of the disease, and the diagnosis of the case of carcinoma of the stomach and pancreas was corroborated post mortem. The case of gastroptosis was sent me by Dr. Babcock, with symptoms suggestive of pancreatitis, but revealing a markedly ptosed stomach on examination. As this condition was the prominent feature, I have classed the case under this head, but it is not unlikely that a pancreatitis may have been associated with the gastroptosis. The fourth case was a diabetic woman, a private patient of Dr. Musser, who had been troubled for some time with irregular attacks of indigestion and constipation. Von Noorden [11] says, " To make a diagnosis of pancreatic diabetes in the absence of symptoms referable to marked pancreatic lesion is most daring "—and although this is very true, the

question of the concurrence of pancreatitis with many cases of diabetes must be borne in mind, even though no symptoms are present (Herzog,[12] Ssobolew [13]).

Four cases of experimental pancreatitis were examined, two of which were positive and two negative. The two cases giving a negative reaction were found at autopsy to show barely discernible evidences of pancreatitis. The two positive cases were typical cases of acute hemorrhagic pancreatitis. Further work is being carried on in this direction, and will be reported in a later paper in collaboration with Dr. Speese.

I have studied but one case of carcinoma of the pancreas *per se*, and this gave a negative reaction, agreeing with Cammidge's results. Of two cases of carcinoma of the stomach with metastases to the pancreas, one was positive and one negative, so of the three cases of pancreatic carcinoma, two were negative, giving a percentage of 33 per cent. positive reactions. Cammidge found four positive reactions in 12 cases of carcinoma of the pancreas, or 33 per cent.

The finding of a positive pancreatic reaction in gallstones associated with pancreatitis is a common occurrence, according to Cammidge, but Schroeder found three negative reactions in four cases of cholelithiasis. My cases are not numerous, but confirm the report of Cammidge.

The cases of cirrhosis of the liver were studied with a special object in view, inasmuch as they were all cases in which an alimentary levulosuria has been found after the ingestion of 100 Gm. of levulose. It has been stated by Steinhaus [14] that the principal reason why cirrhotic cases are not able to utilize levulose is because of the common association of a chronic pancreatitis with the cirrhosis. This was based on post-mortem findings, but has not been generally credited, so it was thought of interest to examine all cirrhotic cases for the pancreatic reaction. As will be seen from the table, ten cases were studied, but with no positive reaction. This would seem to point to another interpretation of alimentary levulosuria, as was mentioned in my preliminary report before the Section on Medicine of the College of Physicians last January.

All cases of glycosuria were examined for the reaction, and in but one case was it obtained.

Conclusions.—Of 62 cases studied, but ten gave a positive reaction. In seven of these the diagnosis was confirmed by operation or autopsy. One case died with all the clinical symptoms of acute pancreatitis, and in the other two a concurrent pancreatic lesion was not improbable. In no cases other than those presenting clinical evidence was a positive reaction obtained.

I firmly believe the test to be a very useful one and to mark a decided advance in the diagnosis of pancreatic disease. The technic is long and complicated and requires great care, but is one that can be readily mastered and is within the scope of any clinician with facilities for laboratory work. Sometimes the end-reaction is obscure on account of crystals forming which are not properly the osazon described by Cammidge, but observation as to structure and their insolubility in 33 per cent. sulphuric acid suffice to render the diagnosis less difficult.

The test is not pathognomonic, and the discoverer himself has never had the temerity to claim this property for it; but taken in connection with the clinical history and examination, and a careful study of the fæces, the Cammidge reaction is strongly suggestive of inflammation of the pancreas.

NOTE.—Since reading this paper I have studied many more cases and have made between 150 and 200 examinations. The results of these observations are in harmony with the above conclusions.

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